REMARKS

Claims 1-23, 25, and 26 were pending in the instant application. By this Amendment, Applicants have canceled claims 15-16 without prejudice. Applicants have amended claims 1-3, 5, 9, 11-12, 17-20, and 25. Applicants have added new claims 27-31. Support for the amendments and new claims can be found in the specification and claims as originally filed. Specifically, support for the amendment to claim 1 can be found, *inter alia*, at page 6, line 32 to page 7, line 1 and page 11, lines 32-35 in the specification, and in originally filed claim 20. Support for the amendment to claim 3 can be found, *inter alia*, in the specification at page 11, lines 12-25 and in originally filed claims 16-17. Claims 5, 9, 11-12 and 17-20 have been amended to change their dependencies. Claim 2 has been amended for clarity. Support for these amendments can be found, *inter alia*, in each of the claims as originally filed. Support for the amendment to claim 25 can be found, *inter alia*, at page 11, lines 12-25. Support for new claims 27-29 can be found, *inter alia*, in originally filed claims 21-23. Finally, support for new claims 30-31 can be found, *inter alia*, at page 8, lines 18-20. Applicants assert that the present Amendment does not introduce any new matter, and thus, its entry is requested. Upon entry of the present Amendment, claims 1-14, 17-23, and 25-31 will be pending and under examination.

Examiner's Withdrawal of Previous Rejections and Objections

The Examiner withdrew the previous objections to claim 19 and to the specification. The Examiner withdrew the previous rejection of claims 1-23 and 25-26 under 35 U.S.C. §112, second paragraph and the previous rejection of claims 1-17, 21-23 and 25-26 under 35 U.S.C.

§103(a).

In response, Applicants acknowledge and appreciate the withdrawal of these objections and rejections.

Substitute Specification

The Examiner indicated that the substitute specification, submitted with the Applicants' previous response (at the request of the Examiner), has not been entered because the Examiner believes it fails to conform with 37 C.F.R. 1.125(a). The Examiner indicated that a statement that the substitute specification contains no new matter is required.

In response, Applicants re-submit the substitute specification, (and marked-up version to show amendments made), as attachments to this Amendment. The substitute specification contains no new matter, and thus its entry is requested.

Examiner's rejections under 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-23 and 25-26 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner stated that the recitation of ". . . the formulation does not contain . . . , any acidic amino acids, arginine, or glycine in amounts of between 0.3 and 5.0% by weight . . . " in claims 1, 3, and 25 represents new matter. The Examiner included claims 2, 4-23, and 26 in this rejection because they depend from the above

independent claims.

In response, without conceding the correctness of the Examiner's position, but to advance prosecution of the subject application, Applicants have amended claims 1, 3, and 25 to remove reference to the language cited by the Examiner. Applicants believe that the amendment of these claims obviates the Examiner's rejection, and thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-23 and 25-26 under 35 U.S.C. § 112, first paragraph.

Examiner's rejections under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 1-23 and 25-26 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Specifically, the Examiner stated that claims 1, 3, and 25 are vague and indefinite for reciting "stability of in vitro biological activity of the formulation . . ." because, in the Examiner's opinion, it is not clear what the biological activity of IFN-β being referred to is in the desired formulation. The Examiner further stated that in vitro antiviral, antiproliferative and immunomodulatory assays are used to assess the biological activity of IFN-β, but it is unclear to the Examiner which of the activities is being retained in the instantly claimed formulation.

In response, Applicants respectfully traverse the Examiner's rejection. One of ordinary skill would clearly know the meaning of the term "biological activity" as it appears in the claims. As the Examiner acknowledges, and as the specification states at page 1, interferons are known to exhibit antiviral, antiproliferative, and immunomodulatory biological activities. Methods for

measuring such biological activity are well known in the art, as the specification sets forth in various places. For example, the specification at page 8, lines 18-31 indicates that "[t]he biological activity after the storage period chosen in each case was measured by the standard method of inhibiting the cytopathic effect of a virus." The specification then proceeds to cite numerous references offering detailed descriptions of the test method. (See also specification at page 13, line 34 to page 14, line 6). Accordingly, Applicants maintain that the term "biological activity" as used in the present claims is not indefinite. Applicants therefore respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-23 and 25-26 under 35 U.S.C. § 112, second paragraph.

Examiner's rejection under 35 U.S.C. § 102

The Examiner rejected claims 1-14 and 21-23 under 35 U.S.C. § 102(b) as allegedly being anticipated by EP 0529300. Specifically, the Examiner stated that the cited reference teaches a liquid formulation of recombinant IFN-β without stabilizing additives, in a buffer at a pH of 7.5, that is stable after 4 weeks when stored at 25° (Examiner cited Example 3, pages 7-8). The Examiner also stated that Example 3 teaches formulations of IFN-β at a concentration of usually 1 x 10^6 to 50 x 10^6 (pages 7-8), setting forth the pH value in the neutral range, with serum proteins such as HSA or PVP as possible additives (page 5, lines 10-11). In the Examiner's opinion, the disclosed range of IFN-β at a concentration of usually 1 x 10^6 to 50 x 10^6 (pages 7-8) (without any added HSA) encompasses the limitations of claims 1, 3, and 25. The Examiner stated that the reference teaches the choices of HSA or PVP, thus making a suggestion of the possible benefits of excluding HSA. The Examiner concluded that the

extended storage life for 3 months at 25° would therefore be an inherent property of the formulation described in the reference. The Examiner further stated that when the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may be an inherent characteristic of the prior art, the Office has authority to require the applicant to prove that the subject matter shown in the art does not possess the characteristics relied on. The Examiner moreover stated that products of identical chemical composition cannot have mutually exclusive properties, and thus, the formulation disclosed in the reference meets the limitations of claim 1-5, 9-14, and 21-23.

In response, Applicants respectfully traverse the Examiner's rejection in light of the claim amendments presented herein. Claim 1, as amended, is directed to a formulation consisting essentially of human interferon-β in a concentration of up to 25 x 10^6 U/ml, a buffer for buffering in a pH range of 5 to 8, and, optionally, at least one physiologically acceptable preservative. Thus, the presence of stabilizers such as human serum albumin (HSA) or polyvinylpyrrolidone (PVP) is excluded. As described in Applicants' specification at pages 5-6, formulations with HSA bring with them higher demands for safety from virus contamination from blood donors. Examples 2, 4, and 5 of EP 0529300 refer to formulations of recombinant IFN-β with human serum albumin. Examples 3 and 6 do not include HSA, but the concentrations of recombinant IFN-β (30 and 70 MU/ml) significantly exceed the upper limit recited in Applicants' claim 1. Accordingly, claim 1 and those depending therefrom are not anticipated by EP 0529300.

Claim 3, as amended, is directed to a formulation that includes methionine. EP 0529300 does not disclose any formulation that includes methionine. Accordingly, claim 3 and those

claims depending therefrom are not anticipated by EP 0529300.

In light of the above remarks and amendments to the claims, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-14 and 21-23 under 35 U.S.C. § 102(b).

Examiner's rejection of claims 1-23, and 25-26 under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-23, and 25-26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over EP 0529300 in view of Patel (U.S. Patent No. 5,358,708). The Examiner referred to the above characterizations of the teachings of EP 0529300, adding that the reference does not recite the specific buffers recited in claims 6-8, the addition of methionine, or the addition of an active ingredient for increasing viscosity or adjusting tonicity.

The Examiner stated that Patel teaches several approaches taken to stabilize and prepare protein formulations of IFN-α, erythropoietin, human plasminogen, IL-2, GM-CSF and plasmin (column 1, paragraph 1-2, claims 1-12 and abstract) with the addition of methionine as a stabilizer. In the Examiner's opinion, it would have been *prima facie* obvious at the time of the invention to prepare an IFN-β formulation as referred to in EP 0529300 with the addition of methionine as taught by Patel to prevent oxidation, and the motivation for doing so would be because Patel teaches in Figure 4 that the addition of methionine is effective in extending the storage life of IFN-α-2b (Example 1, lines 35-47). The Examiner further stated that one of skill in the art would be motivated to stabilize IFN-β to be used for therapy so that at prolonged periods at nearly room temperature and a pH close to neutral (similar to body fluids), the IFN-β can be stored until it is administered.

In response, Applicants respectfully traverse the Examiner's rejection. The Examiner acknowledges that Patel teaches IFN-α-2b formulations, not IFN-β formulations. Applicants also point out that Patel itself states at column 2, lines 52-57, that the three major human interferons that have been identified, namely interferon-α, interferon-β, and interferon-γ, each possess different antigenic and physicochemical properties and are derived from different cellular sources, in response to different inducers. Therefore, Patel's disclosure of any particular stabilizers effective in extending storage life of IFN-α-2b formulations does not result in an expectation that the same effectiveness would occur in IFN-β formulations. At most, Patel's teaching would represent an obviousness to try various choices until possibly arriving at a successful result. Such an "obvious to try" standard is improper in support of an obviousness rejection. Even if one were to try one of the interferons referred to in Patel in Applicants' formulation, there would be no reasonable expectation of success of such a combination, based on any teaching either in Patel or in the art. Moreover, with respect to claim 1, one of skill in the art could not have expected a low concentrate IFN-β formulation (i.e. activity up to 25 MU/ml, such as claimed by Applicants), in the absence of stabilizers, to exhibit high stability of in vitro biological activity. Low concentration protein solutions had a known tendency to produce instability and it was therefore believed that they needed to be stabilized by the addition of stabilizers or by the establishment of a non-physiological pH value. This is particularly applicable with respect to IFN-β, as can be seen from the instant specification at page 2, line 26 to page 4, line 26.

With respect to claim 3, Applicants further point out that Patel's Figure 1 indicates that IFN-α, (as opposed to GM-CSF (Fig. 2) and IL4 (Fig. 4), shows a significant decrease in

biological activity after two weeks' storage, despite the addition of methionine or histidine. This is so even with a very high concentration of methionine (20 mg/10ml, corresponding to 13.33 mmol/ml). Accordingly, based on the prior art, one skilled in the art could not reasonably have expected the increase in stability of IFN-β in pharmaceutically suitable concentrations from the addition of methionine, that is exhibited by the Applicants' claimed invention. Therefore, the claimed invention is not obvious over EP 0529300 or Patel, either alone or in combination, and thus, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-23, and 25-26 under 35 U.S.C. § 103(a).

In view of the above remarks and amendments, Applicants believe that the Examiner's rejections set forth in the February 7, 2003 Office Action have been fully overcome and that the present application is in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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Attachment: Substitute Specification (re-submitted)